EXHIBIT 1

FOREIGN LANGUAGE EDITIONS
of The Merck Manual

Arabic—Larike Publications Services, Cyprus
Chinese—People's Medical Publishing House, Beijing
Czech—Egem, Prague
French—Editions d'Apres, Paris
German—Urban & Schwarzenberg, GmbH, Munich
Greek—Medical & Scientific Publishing, Athens
Hungarian—Melania, Budapest
Italian—Stampa Medica, s.p.a., Rome
Japanese—Medical Book Service Ltd., Naka-Ku Nagoya
Polish—Urban & Partner, Wroclaw
Portuguese—Editora Roca, Ltda, São Paulo
Russian—MIR Publishers, Moscow
Spanish—Harcourt Brace, Barcelona
Turkish—Yüce, Istanbul

OTHER MERCK BOOKS

THE MERCK INDEX
First Edition, 1889

THE MERCK VETERINARY MANUAL
First Edition, 1955

THE MERCK MANUAL OF GERIATRICS
First Edition, 1990

THE MERCK MANUAL OF MEDICAL INFORMATION—HOME EDITION
First Edition, 1997

Merck books are published on a nonprofit basis as a service to the scientific community and the public.

SEVENTEENTH EDITION

THE MERCK MANUAL

OF

DIAGNOSIS AND THERAPY

Editors
MARK H. BEERS, M.D., and ROBERT BERKOW, M.D.

Senior Assistant Editors
ROBERT M. BOGIN, M.D., and
ANDREW J. FLETCHER, M.B., B.Chir.

Editorial Board
Philip K. Bondy, M.D.
Preston V. Dilts, Jr., M.D.
Douglas A. Drossman, M.D.
L. Jack Falling, M.D.
Eugene P. Frenkel, M.D.
Glen O. Gabbard, M.D.
Robert A. Hoeckelman, M.D.
Gerald L. Mandell, M.D.
Fred Plum, M.D.
G. Victor Rossi, Ph.D.
Paul H. Tanser, M.D., F.R.C.P.(C)

Published by MERCK RESEARCH LABORATORIES
Division of MERCK & CO., INC.
Whitehouse Station, N.J. 1999

cooperation and collaboration among the personalities and to reduce symptoms. This treatment is often arduous and painful, and many crises tend to arise as a result of the personalities' actions and the patient's despair when dealing with traumatic memories. One or more periods of psychiatric hospitalization may be necessary to help some patients through difficult times and during the processing of particularly painful memories. Hypnosis is often used to help access the personalities, facilitate communication between them, and stabilize and interpret them. Hypnosis is also used to discuss traumatic memories and diffuse their impact. Eye movement desensitization and reprocessing (EMDR), applied cautiously, is a useful adjunct. EMDR tries to process traumatic memories and to replace negative thoughts about self that are associated with these memories with positive ones.

Generally, two or more psychotherapy sessions per week for 3 to ≥ 6 years are necessary to integrate the personalities or to achieve harmonious interaction among them that allows normal functioning without symptoms. Integration of the personalities is the most desirable outcome.

Psychotherapy has three main phases. In the first phase, the priority is safety, stabilization, and strengthening of the patient in anticipation of the difficult work of processing traumatic material and dealing with problematic personalities. The personality system is explored and mapped to plan the remainder of the treatment. In the second phase, the patient is helped to process the painful episodes of his past and to mourn the losses and other negative consequences of the trauma. As the reasons for the patient's remaining dissociations are addressed, therapy can move to the final phase, in which the patient's selves and relationships and social functioning can be reconnected, integrated, and rehabilitated. Some integration occurs spontaneously, but much must be encouraged by conversing with and arranging the unification of the personalities or must be facilitated with imagery and hypnotic suggestion. After integration, patients continue treatment to deal with some issues that have not been resolved. After postintegration treatment appears complete, visits to the therapist are tapered but are rarely completely terminated. Patients come to think of the psychiatrist as someone who can help them deal with psychologic issues, just as they periodically need assistance from a primary care physician.

DEPERSONALIZATION DISORDER

Persistent or recurrent feelings of being detached from one's body or mental processes and usually a feeling of being an outside observer of one's life.

Depersonalization is the third most common psychiatric symptom and frequently occurs in life-threatening danger, such as accidents, assaults, and serious illnesses and injuries; it can occur as a symptom in many other psychiatric disorders and in seizure disorders. As a separate disorder, depersonalization has not been studied widely, and its incidence and cause are unknown.

Symptoms and Diagnosis

Patients have a distorted perception of themselves, their bodies, and their lives, which makes them uncomfortable. A person may feel as if he is an automaton or is in a dream. Often the symptoms are transient and occur with anxiety, panic, or phobic symptoms. However, symptoms can be chronic and persist or recur for many years. Patients often have great difficulty describing their symptoms and may fear or believe the symptoms mean they are going crazy. The patient often feels unreal and may experience the world as unreal and dreamlike.

Some patients are minimally impaired; others become severely compromised or even disabled. Although some can adjust to depersonalization disorder or even block its effect, others have chronic anxiety about their state of mind, worry whether they are going crazy, or ruminate on the implications of their distorted perceptions of their bodies and their sense of estrangement from themselves and the world.

Diagnosis is made based on the symptoms. The physician must rule out physical disorders, substance abuse, and other dissociative disorders. Psychologic tests and special interviews are helpful.

Prognosis and Treatment

Complete recovery is possible for many patients, especially those whose symptoms occurred in connection with stresses that can be dealt with in treatment. Other patients do not respond well to treatment but may gradually improve on their own.

The feeling of depersonalization is often transient and resolves spontaneously. Treatment is warranted only if the disorder is persistent, recurrent, or distressing. Various psychotherapies (eg, psychodynamic psychotherapy, cognitive behavior therapy, hypnosis) are successful for some patients, but no one treatment has proved effective for all. Tranquilizers and antidepressants have helped some patients. Other psychiatric disorders, which are often associated with or precipitated by depersonalization, must be treated. Treatment must address all stresses associated with the onset of the disorder.

189 / MOOD DISORDERS

(Affective Disorders)

A group of heterogeneous, typically recurrent illnesses including unipolar (depressive) and bipolar (manic-depressive) disorders that are characterized by pervasive mood disturbances, psychomotor dysfunction, and vegetative symptoms.

(For mood disorders in children, see Ch. 274.)

Current diagnostic practice emphasizes depression and elation as the core affective components of mood disorders. However, anxiety and irritability are equally common, explaining the continued popularity of the broader rubric "affective disorder," the previous official designation.

Sadness and joy are part of everyday life and should be differentiated from clinical depression and morbid elation. Sadness, or normal depression, is a universal human response to defeat, disappointment, and other adverse situations; the response may be adaptive by permitting withdrawal to conserve inner resources. Transient depression ("blues") may occur as a reaction to certain holidays or significant anniversaries, during the premenstrual phase, and during the first 2 wk postpartum. Such reactions are not abnormal, but persons predisposed to depression may break down during such times.

Grief (normal bereavement), the prototype of **reactive depression**, occurs in response to significant separations and losses (eg, death, marital separation, romantic disappointment, leaving a familiar environment, forced emigration, or civilian catastrophes). Grief may be manifested by anxiety symptoms, such as insomnia, restlessness, and autonomic nervous system hyperactivity. Like other adversities, separations and losses generally do not cause clinical depression, except in persons predisposed to a mood disorder.

Elation, usually linked to success and achievement, is sometimes considered a defense against depression or a denial of the pain of loss (eg, a rare form of bereavement reaction in which elated hyperactivity may completely replace the expected grief). In predisposed persons, such reactions may lead to mania. **Paradoxical depression** may follow positive events, possibly because the associated increased responsibilities often have to be faced alone.

Depression or mania is diagnosed when sadness or elation is overly intense and continues beyond the expected impact of a life stressor or arises in the absence of a stressor. Symptoms and signs often cluster into discrete syndromes that typically recur or, less commonly, persist without remission. Clinical depression and mania, unlike normal emotional reactions, cause marked impairment in physical function, social function, and work capacity.

Epidemiology

Some type of mood disturbance, which may require clinical attention, affects 20% of women and 12% of men during their lifetime. These figures largely represent unipolar major depressive disorder and its variants. Although the incidence of bipolar disorder in the general population was estimated at < 2%, new estimates are closer to 4 to 5%. Depression affects twice as many women as men; bipolar disorder affects the sexes

equally, but depressive forms predominate in women and manic forms in men. Bipolar disorder usually begins in the teens, 20s, or 30s; unipolar disorders begin, on average, in the 20s, 30s, or 40s. Persons born in the 2 decades after World War II have higher rates of depression and suicide, often associated with higher rates of substance abuse, than those born earlier. Female sex is the major demographic risk factor for depression; social class, culture, and race have not been consistently associated with depression. However, bipolar disorder is somewhat more common in upper socioeconomic classes. Cultural factors seem to modify the clinical manifestations of mood disorders. For example, physical complaints, worry, tension, and irritability are more common manifestations in lower socioeconomic classes; guilty ruminations and self-reproach are more characteristic of depression in Anglo-Saxon cultures; and mania tends to manifest itself more floridly in some Mediterranean and African countries and among black Americans. Economic factors, such as unemployment and sudden financial reversals, have been linked to increased suicide rates in men.

Mood disorders are the most prevalent psychiatric disorders, accounting for 25% of patients in public mental institutions, 65% of psychiatric outpatients, and as many as 10% of all patients seen in nonpsychiatric medical settings.

Etiology

Primary mood disorders: The interaction of several factors contributes to these disorders. **Heredity** is the most important predisposing factor. The precise mode of inheritance is uncertain, but dominant genes (X-linked or autosomal) may be involved in some forms of bipolar disorder. Polygenic inheritance as a common genetic substrate for bipolar and recurrent unipolar disorders is a more popular hypothesis. What is inherited is unknown. But the final common pathway of mood disorders is believed to be impaired limbic-diencephalic function; recent brain imaging studies further implicate subcortical extrapyramidal structures and their prefrontal connections. Cholinergic, catecholaminergic (noradrenergic or dopaminergic), and serotonergic (5-HT) neurotransmission appears to be dysregulated. Heredity may also increase the likelihood of depression by exposing children to the negative effects of their parent's mood disorders (eg, disruption of affective bonds).

Childhood loss of a parent does not increase a person's risk of developing a mood disorder. However, if such a person develops a mood disorder, depression tends to develop at a younger age and follow a chronically intermittent course, leading to marked personality disturbance and suicide attempts.

Stressors that provoke affective episodes can be psychologic or biologic. Traumatic life events, especially separations, commonly precede depressive and manic episodes; however, such events may represent the prodromal manifestations of a mood disorder rather than its cause (eg, affectively ill persons often alienate their loved ones). The switch from depression to mania is often heralded by reduced sleep for 1 to 3 days and can be experimentally induced by sleep deprivation, particularly of rapid eye movement (REM) sleep. Such a switch commonly follows therapy with antidepressants. Stimulant use, sedative-hypnotic withdrawal, transmeridian travel, and seasonal changes in light may also induce mania.

Although persons with any personality type can develop clinical depression, it is more common in persons with **temperaments** inclined to dysthymia and cyclothymia. Unipolar depression is more likely to develop in persons who are introverted and have anxious tendencies. Such persons often lack the requisite social skills to adjust to significant life pressures and have difficulty recovering from a depressive episode. Persons with bipolar disorders tend to be extroverted and achievement-oriented; they often use activity to combat depression.

Female sex as a risk factor for depression is customarily explained by women's presumed more affiliative nature, dependency traits, and helplessness in controlling their destiny in male-oriented societies. However, biologic vulnerabilities are also relevant. Having two X chromosomes is important in bipolar disorders if dominant X-linkage is involved. Compared with men, women have higher levels of monoamine oxidase (the enzyme that degrades neurotransmitters considered important for mood). Thyroid function is more commonly dysregulated in women. Women may use oral contraceptives containing progesterone, believed to be a de-

TABLE 189–1. SOME CAUSES OF SYMPTOMATIC DEPRESSION AND MANIA

Type of Cause	Depression	Mania
Collagen-vascular	SLE	SLE Rheumatic chorea
Endocrinologic	Hyperthyroidism and hypothyroidism Addison's disease Cushing's disease Diabetes mellitus Hyperparathyroidism Hypopituitarism	Hyperthyroidism
General medical	Coronary artery disease Fibromyalgia Renal or hepatic failure	
Infectious	AIDS General paresis (tertiary syphilis) Influenza Infectious mononucleosis Tuberculosis Viral hepatitis Viral pneumonia	AIDS General paresis (tertiary syphilis) Influenza St. Louis encephalitis
Neoplastic	Cancer of the head of the pancreas Disseminated carcinomatosis	
Neurologic	Complex partial seizures (temporal lobe) Head trauma Multiple sclerosis Stroke (left frontal) Cerebral tumors Parkinson's disease Sleep apnea	Complex partial seizures (temporal lobe) Head trauma Multiple sclerosis Stroke Diencephalic tumors Huntington's chorea
Nutritional	Pellagra Pernicious anemia	
Pharmacologic	Amphetamine withdrawal Steroids Anticholinesterase insecticides Barbiturates Cycloserine, amphotericin B Indomethacin, cimetidine Metoclopramide Phenothiazines Reserpine Thallium, mercury Vincristine, vinblastine	Amphetamines, methylphenidate Steroids Antidepressants (most) Cocaine Levodopa, bromocriptine Sympathomimetic drugs
Psychiatric	Alcoholism and other substance use disorders Antisocial personality Dementing disorders in the early phase Schizophrenic disorders	

pressant, and undergo premenstrual and postpartum endocrine changes. Depressed women are more likely to exhibit the introverted, brooding/inhibited personality style typical of unipolar disorders, whereas depressed men are significantly more likely to exhibit the extroverted, action-oriented personality style typical of bipolar disorders.

Secondary mood disorders: Often, a mood disorder develops in association with a nonaffective disorder via a physiologic or psychologic mechanism or both (see TABLE 189–1). Some disorders, such as myxedema depression, result from physiochemical factors and are considered symptomatic depressions. Others, such as the depression that accompanies debilitating cardiopulmonary disorders, are usually explained as depressive reactions to the underlying disorder. Often, both mechanisms are operative (eg, in patients with AIDS who have cerebral dysfunction and profound sadness). Bipolar disorder rarely complicates another psychiatric disorder; if alcohol or substance use precedes a bipolar disorder, it is most likely an attempt to self-treat the prodromal manifestations of the disorder.

The foregoing findings concerning nonaffective disorders and drugs that produce depression suggest that the pathogenesis for all mood disorders forms a continuum and that the distinction between primary and secondary mood disorders is arbitrary. All patients who meet the criteria for a mood disorder must be treated regardless of whether other disorders are present and no matter how understandable the depression seems in light of the underlying disorder.

Risk of Suicide

Suicide, the most serious complication in patients with mood disorders, is the cause of death in 15 to 25% of untreated patients with mood disorders; unrecognized or inadequately treated depression contributes to 50 to 70% of all completed suicides. Suicide, which is most common in young and elderly men who do not have good social support, tends to occur within 4 to 5 yr of the first clinical episode. The immediate recovery phase from depression (when psychomotor activity is returning to normal, but the mood is still dark), mixed bipolar states, the premenstrual state, and personally significant anniversaries are major risk periods (see also Ch. 190). Concurrent alcohol and substance abuse also increases the risk of suicide. Serotonin dysfunction appears to be one of the biochemical factors in suicide, and prophylaxis with lithium (which stabilizes the serotonin system) is effective in suicide prevention.

Of drugs prescribed for mood disorders, an overdose with a heterocyclic antidepressant or lithium (see also TABLE 307–3) is most likely to be life threatening; alcohol is often a complicating factor. Heterocyclic antidepressant overdose causes a hyperactive coma with atropinism; cause of death is usually cardiac arrhythmia or status epilepticus. Because of protein-binding, forced diuresis and hemodialysis are useless, and treatment focuses on stabilizing cardiac and cerebral function. For lithium overdose, forced diuresis with sodium chloride or mannitol, alkalinization of urine, and hemodialysis may be lifesaving. Monoamine oxidase inhibitors, less commonly prescribed now, rarely result in overdose. Newer antidepressants (eg, selective serotonin reuptake inhibitors, venlafaxine, nefazodone, mirtazapine, bupropion) appear to be usually nonfatal in suicidal overdose—one of their major advantages.

Diagnosis

Diagnosis is based on the symptomatic picture (see TABLE 189–2), course, family history, and, sometimes, the unequivocal response to somatic interventions. Secondary medical or neurologic causes should be excluded, especially after age 40.

There are no pathognomonic laboratory findings in mood disorders. Tests for limbic-diencephalic dysfunction, such as the thyrotropin-releasing hormone (TRH) stimulation test, the dexamethasone suppression test (DST), and sleep EEG for rapid eye movement (REM) latency, are sometimes used in academic settings. There is no consensus on the diagnostic sensitivities and specificities of these tests, and the tests are not useful for screening. A negative test result does not exclude a depressive disorder; a positive result is more significant clinically.

Diagnosis of depression may be difficult when anxiety symptoms are the prominent presentation (see TABLE 189–3). Excessive worrying, panic attacks, and obsessions are common in primary depressive disorders and disappear when the depressive episode remits. Conversely, in primary anxiety disorders, these symptoms usually fluctuate irregularly and remission of depressive symptoms typically does not eliminate them. Prominent anxiety symptoms first appearing after age 40 most likely represent a primary mood disorder.

TABLE 189–2. MANIFESTATIONS OF DEPRESSION AND MANIA

Manifestation	Depressive Syndrome	Manic Syndrome
Mood changes	Depressed, irritable, or anxious (however, some patients smile or deny subjective mood change and instead complain of pain, other somatic distress, or fears) Crying spells (however, some patients complain of the inability to cry or to experience emotions)	Elated, irritable, or hostile Momentary tearfulness (as part of mixed state)
Cognitive and psychologic disturbances	Lack of self-confidence, low self-esteem, self-reproach Poor concentration, indecisiveness Reduced gratification, loss of interest in usual activities, loss of attachments, social withdrawal Negative expectations, hopelessness, helplessness, increased dependency Recurrent thoughts of death and suicide	Inflated self-esteem, boasting, grandiosity Racing thoughts, clang associations (new thoughts triggered by word sounds rather than meaning), distractibility Heightened interest in new activities, increased involvement with people (who are often alienated because of the patient's intrusive and meddlesome behavior), buying sprees, sexual indiscretions, foolish business investments
Psychomotor and vegetative dysfunction	Psychomotor retardation, fatigue Agitation Anorexia and weight loss or weight gain Insomnia or hypersomnia Menstrual irregularities, amenorrhea Anhedonia, loss of sexual desire	Psychomotor acceleration, eutonia (increased sense of physical fitness) Possible weight loss from increased activity and inattention to proper dietary habits Decreased need for sleep Increased sexual desire
Psychotic features	Delusions of worthlessness and sinfulness Delusions of reference and persecution Delusions of ill health (nihilistic, somatic, or hypochondriacal) Delusions of poverty Depressive auditory, visual, and (rare) olfactory hallucinations	Grandiose delusions of exceptional talent Delusions of assistance or of reference and persecution Delusions of exceptional physical fitness Delusions of wealth, aristocratic ancestry, or other grandiose identity Fleeting auditory or visual hallucinations

Mixed anxiety-depression (anxious depression) refers to conditions in which mild symptoms common to anxiety and mood disorders are present. They usually pursue a chronically intermittent course. Because of the greater gravity of depressive disorders and the risk of suicide, patients with mixed anxiety-depression should be treated for depression. Obsessions, panic, and social phobias with hypersomnic depression suggest bipolar II disorder.

In the elderly, **depressive pseudodementia** is associated with psychomotor retardation, decreased concentration, and memory impairment and therefore may be confused with early dementia, which often begins with affective changes (see DEMENTIA

TABLE 189–3. PROFILES OF ANXIETY AND DEPRESSION

Anxiety	Depression
Hypervigilance	Psychomotor retardation
Severe tension and panic	Severe sadness
Perceived danger	Perceived loss
Phobic avoidance	Loss of interest (anhedonia)
Doubt and uncertainty	Hopelessness, suicidal preoccupation
Insecurity	Self-depreciation
Performance anxiety	Loss of libido
	Early morning awakening
	Weight loss

Reprinted from Akiskal HS: "Toward a clinical understanding of the relationship of anxiety and depressive disorders," in *Comorbidity of Mood and Anxiety Disorders*, edited by JP Maser and CR Cloninger. Washington, DC, American Psychiatric Press, 1990, p. 597; used with permission.

in Ch. 171). In general, when the diagnosis is uncertain, treatment of depressive disorder should be tried, because of its better prognosis. Several features (see TABLE 189–4) can help in differential diagnosis.

The terms **masked depression** and **affective equivalents** are often used to explain prominent physical symptoms (eg, headache, fatigue, insomnia) or behavioral disturbance when mood change is minimal or absent. Affective equivalents include antisocial acting out (especially in children and adolescents), impulsive risk taking, gambling, chronic pain, hypochondriasis, anxiety states, and so-called psychosomatic disorders. Without core affective symptoms, the diagnosis of a mood disorder is not appropriate unless affective episodes have occurred in the past, the condition recurs periodically, and the family history includes mood disorders. Because diagnosis may be difficult, therapeutic trials with antidepressants and/or mood stabilizers are often conducted.

Differentiating chronically intermittent mood disorders, such as cyclothymia and dysthymia, from **substance use disorders** is difficult. Unipolar depression is a less common cause of alcoholism and drug abuse than was once thought (see Ch. 195). Depressed and manic patients may use alcohol or drugs in an attempt to treat sleep disturbances, and manic patients may seek drugs (eg, cocaine) to enhance excitement, usually with catastrophic effects on their illness. Toxic effects of drugs, drug withdrawal, or social complications may accompany substance use disorders, causing transient or intermittent depression. Episodic substance abuse, especially of alcohol (dipsomania), or onset after age 30 suggests diagnosis of a primary mood disorder with secondary substance abuse. When the diagnosis is in doubt, a therapeutic trial with antidepressant or mood-stabilizing drugs can often be defended clinically.

TABLE 189–4. DIFFERENTIATING DEPRESSIVE PSEUDODEMENTIA FROM PRIMARY (DEGENERATIVE) DEMENTIA

Clinical Features	Pseudodementia	Primary Dementia
Onset	Acute	Insidious
Past affective episodes	Common	Uncharacteristic
Self-reproach	Common	Uncharacteristic
Diurnality	Worse in morning	Worse at night
Memory deficit	Equal for recent and remote	Greater for recent than for remote
Other cognitive deficits	Circumscribed	Global
Response to cognitive testing	"Don't know"	Near miss
Reaction to mistakes	Tend to give up	Catastrophic
Practice effects	Can be coached	Consistently poor
Response to sleep deprivation	Improvement	Worsening (?)

Modified from Akiskal HS: "Mood disturbances," in *Medical Basis of Psychiatry*, ed. 2, edited by G Winokur and P Clayton. Philadelphia, WB Saunders Company, 1994, pp. 365–379; used with permission.

TABLE 189–5. DIFFERENTIATING AFFECTIVE AND SCHIZOPHRENIC PSYCHOSES

Criteria	Affective Psychosis	Schizophrenic Psychosis
Age at onset	Any age	Rarely after age 40 yr
Premorbid traits	Anxiety-prone, dysthymic, cyclothymic, or hyperthymic	Schizoid or schizotypal
Onset	Usually abrupt	Usually insidious
Affect	Usually "infectious"	Rigid, blunted, or inappropriate
Thought processes	Usually intelligible; slowed down or accelerated	Typically difficult to follow (loose associations)
Delusions and hallucinations	Usually mood-congruent, but incidental schneiderian symptoms can also occur	Typically idiosyncratic, bizarre, and affecting multiple areas of the patient's life; commonly schneiderian in form
Family history	Mood disorder, alcoholism	Schizophrenia
Course	Usually remitting or periodic; personality generally preserved	Usually unremitting; social functioning often deteriorated

Updated from Akiskal HS, Puzantian VR: "Psychotic forms of depression and mania." *Psychiatric Clinics of North America* 2(3):419–439, 1979; used with permission.

Differentiating between affective psychosis and **schizophrenia** or **schizoaffective disorder** (see Ch. 193) may be difficult because many schizophrenic features (eg, mood-incongruent delusions or hallucinations) occur in mood disorders. The correct diagnosis is important because lithium may cause neurotoxicity in schizophrenia, and neuroleptics may cause tardive dyskinesia in mood disorders. Diagnosis must be based on the overall clinical picture, family history, course, and associated features (see TABLE 189–5). Alcoholic hallucinosis, sedative-hypnotic withdrawal, psychedelic-induced psychosis, and other systemic or brain disorders may also produce psychotic symptoms. Diagnosis of a schizoaffective disorder should not be made until such complicating factors are excluded. When the diagnosis is in doubt, a therapeutic trial with an antidepressant, a mood stabilizer, or electroconvulsive therapy is indicated, because of the better prognosis of mood disorders.

Differentiating mood disorders from severe **personality disorders** (eg, borderline personality) is also difficult, especially when the mood disorder has a chronic or intermittent course—eg, dysthymia, cyclothymia, or bipolar II disorder. Past course with affective manifestations, especially when biphasic, and a family history of mood disorders support a diagnosis of mood disorder. Some laboratory findings (especially REM latency and TRH stimulation) in patients with borderline personality disorder and in those with mood disorder are similar; this similarity can be interpreted to mean that the two disorders are related or that these tests are not helpful in differential diagnosis. Some experts believe that at least some forms of borderline personality disorder represent a mood disorder variant, but this theory is controversial. For young patients pursuing a tempestuous, impulsive course that could culminate in serious suicide attempts, a trial with thymoleptic and mood-stabilizing drugs conducted by experts in a controlled setting—a hospital or mood clinic—is recommended.

DEPRESSION

(Unipolar Disorder)

In its full syndromal expression, clinical depression manifests as **major depressive disorder,** with episodic course and varying degrees of residual manifestations between episodes.

Symptoms, Signs, and Diagnosis

The mood is typically depressed, irritable, and/or anxious. The patient may appear miserable, with furrowed brows, downturned corners of the mouth, slumped posture, poor

eye contact, and monosyllabic (or absent) speech. The morbid mood may be accompanied by preoccupation with guilt, self-denigrating ideas, decreased ability to concentrate, indecisiveness, diminished interest in usual activities, social withdrawal, helplessness, hopelessness, and recurrent thoughts of death and suicide. Sleep disorders are common. In some, the morbid mood is so deep that tears dry up; the patient complains of an inability to experience usual emotions—including grief, joy, and pleasure—and of a feeling that the world has become colorless, lifeless, and dead. For such patients, being able to cry again is usually a sign of improvement.

Melancholia (formerly **endogenous depression**) has a qualitatively distinct clinical picture, characterized by marked psychomotor slowing (of thinking and activity) or agitation (eg, restlessness, wringing of the hands, pressure of speech), weight loss, irrational guilt, and loss of the capacity to experience pleasure. Mood and activity vary diurnally, with a nadir in the morning. Most melancholic patients complain of difficulty falling asleep, multiple arousals, and insomnia in the middle of the night or early morning. Sexual desire is often diminished or lost. Amenorrhea can occur. Anorexia and weight loss may lead to emaciation and secondary disturbances in electrolyte balance.

Some experts consider psychotic manifestations, which occur in 15% of melancholic patients, the hallmark of a **delusional or psychotic depressive subtype.** Patients have delusions of having committed unpardonable sins or crimes; hallucinatory voices accuse them of various misdeeds or condemn them to death. Visual hallucinations (eg, of coffins or deceased relatives) occur but are uncommon. Feelings of insecurity and worthlessness may lead some patients to believe that they are being observed or persecuted. Others think that they harbor incurable or shameful disorders (eg, cancer, sexually transmitted disease) and that they are contaminating other persons. Very rarely, a person with psychotic depression kills family members—including infants—to "save" them from future misfortune and then commits suicide. Dexamethasone suppression test results are consistently positive in patients with psychotic depression.

In **atypical depression,** reverse vegetative features dominate the clinical presentation; they include anxious-phobic symptoms, evening worsening, initial insomnia, hypersomnia that often extends into the day, and hyperphagia with weight gain. Unlike patients with melancholia, those with atypical depression show mood brightening to potentially positive events but often crash into a paralyzing depression with the slightest adversity. Atypical depressive and bipolar II disorders overlap considerably.

The diagnosis of clinical depression is usually straightforward, but recognizing low-grade symptoms may be difficult. For example, in major depressive disorder with incomplete recovery, classic depressive symptoms recede and are replaced by subacute or chronic hypochondriacal concerns, irritable morosity, and secondary interpersonal trouble in conjugal life. In other patients, considered **masked depressives,** depression may not be consciously experienced. Instead, patients complain of being physically ill and may wear a defensive mask of apparent cheerfulness (smiling depression). Others complain of fatigue, various aches and pains, fears of calamity, and fears of becoming insane. REM latency is shortened in these patients, supporting the affective nature of the clinical presentations.

Diagnosis is based on the cluster of symptoms and signs described above and should be considered in all patients, particularly those who say that they do not deserve to be treated or refuse to cooperate with medically needed procedures or treatments.

Treatment

General principles: Most persons with depression are treated as outpatients. Pharmacotherapy, delivered in the context of supportive therapy and psychoeducation (see below), is the treatment of choice for moderate to severe depression; milder depression can be treated with psychotherapy. All patients with depression must be asked gently but directly about suicidal ideation, plans, or activity. All communication of self-destruction should be taken seriously.

Initially, the physician sees patients with depression weekly or biweekly to provide support and education about the disorder and to monitor progress. During the early phase of treatment, keeping in touch with the patient and family via a few telephone calls may help. Because many are embarrassed and demoralized by having a mental disorder, the patient, his family, and his employer (when appropriate and after obtaining informed consent from the patient) should be told that most often, depression is a self-limiting medical disorder with a good prognosis. Some patients may find the diagnosis of depression unacceptable, and the physician should reassure them that depression does not reflect a character flaw, giving some explanation of the biologic disturbances of depression. Patients who are concerned about "taking drugs" can be reassured that antidepressants are not habit-forming. Telling patients that the path to recovery often fluctuates helps reduce demoralization and ensure compliance. Treatment of depressive episodes with drugs should continue for at least the natural duration of an episode (ie, 6 mo).

Specific advice to patients often helps. It includes telling them to be as active as possible, but to not take on insurmountable tasks; to try to be with other people; not to blame themselves for being depressed; and to remember that dark thoughts are part of the illness and will go away. Significant others should be told that depression is a serious illness requiring specific treatment; patients with depression are not lazy; loss of love or job is often the result, not the cause of depression; religion may comfort but does not cure; exercise is not a treatment specifically geared for depression; and vacations may make depression worse.

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, sertraline, paroxetine, and fluvoxamine (see TABLE 189–6).

The following principles help in understanding how SSRIs and other new antidepressants affect the serotonin (5-hydroxytryptamine [5-HT]) system. Presynaptic 5-HT blockade results in more 5-HT to stimulate many postsynaptic 5-HT receptors. Stimulation of 5-HT_1 receptors is associated with antidepressant and anxiolytic effects. Stimulation of 5-HT_2 receptors produces nervousness, insomnia, and sexual dysfunction, and blockade is associated with alleviation of depression. Stimulation of 5-HT_3 receptors is associated with nausea and headache, and blockade reverses the nausea.

By preventing the reuptake of 5-HT presynaptically, SSRIs ultimately lead to more efficient central 5-HT function. They lack anticholinergic, adrenolytic, and cardiac conduction effects. Although selective to the 5-HT system, SSRIs are not specific in their actions on different 5-HT receptors. Thus, while 5-HT_1 stimulation results in antidepressant and anxiolytic effects, 5-HT_2 and 5-HT_3 stimulation results in the common SSRI adverse effects of nausea, anxiety, insomnia, headache, restlessness, and sexual dysfunction. So, paradoxically, SSRIs can both relieve and cause anxiety. Anorexia can occur in the first few months, especially with fluoxetine; the weight loss can be useful for overweight and bulimic patients. Sedation is minimal or nonexistent, but some patients tend to be sleepy during the day in the early weeks of treatment. Agitation may necessitate discontinuation in 3 to 4% of patients. Rarely, akathisia occurs (due to feeble dopaminergic activity?). The most common adverse effects are sexual (eg, decreased libido, difficult orgasm), occurring in up to 1/3 of patients. Some patients accept these effects as the price for relief of depression, but 1 in 10 patients request or need to be switched to another class of antidepressant. Other adverse effects are loose stools and headache. Drug interactions are uncommon. SSRIs are safe in overdose, have a wide therapeutic margin, and are relatively easy to administer, with little need for dose adjustment (except for fluvoxamine). The success of these drugs has contributed to the wide acceptance of antidepressant treatment of depression by patients.

SSRIs are also indicated in depression-related disorders in which heterocyclic antidepressants are not as effective, including dysthymic disorder, atypical depression, seasonal depression, obsessive-compulsive disorder, social phobia, bulimia, premenstrual syndrome, and possibly borderline personality disorder.

Nefazodone, which blocks primarily the 5-HT_2 receptor, also inhibits reuptake of 5-HT and norepinephrine. The result is antidepressant and anxiolytic action without sexual dysfunction, and nausea is not a problem because nefazodone also blocks 5-HT_3 receptors. Unlike most antidepressants, nefazodone does not suppress REM sleep and produces restful sleep. However, serious cardiac arrhythmias may develop with concurrent use of terfenadine or astemizole.

Trazodone, an antidepressant related to nefazodone, is a 5-HT_2 receptor blocker, but it does not inhibit 5-HT reuptake presynap-

TABLE 189–6. ANTIDEPRESSANTS MARKETED IN THE USA

Class	Drug	Dose Range (mg/day)	Precautions
Heterocyclic antidepressants			As a class, contraindicated in patients with heart disease, angle-closure glaucoma, prostatic hypertrophy, or esophageal hiatus hernia; falls due to postural hypotension can lead to fractures in the frail elderly; potentiates the effect of alcohol; raises blood level of antipsychotic drugs
	Amitriptyline	50–300	Causes weight gain
	Nortriptyline	25–100	Effective within therapeutic window
	Imipramine	50–300	May cause excessive sweating and nightmares
	Desipramine	50–300	Not to be used in patients < 12 yr old
	Doxepin	25–300	Causes weight gain
	Trimipramine	50–300	Causes weight gain
	Clomipramine	25–225	Lowers seizure threshold at doses of > 250 mg/day
	Protriptyline	15–60	Difficult to dose because of complex pharmacokinetics
	Amoxapine	150–400	Can cause extrapyramidal adverse effects
	Maprotiline	75–225	May provoke suicidal behavior
MAOIs			Serotonergic syndrome possible when taken with an SSRI or nefazodone; hypertensive crisis possible when taken with other antidepressants, sympathomimetic or other selective drugs, or certain foods and beverages
	Phenelzine	45–90	Causes postural hypotension
	Tranylcypromine	20–60	Has amphetamine-type stimulant effects and modest abuse potential
SSRIs	Fluoxetine	10–60	Even after fluoxetine is withdrawn, because of its long half-life, it has a greater potential for interactions between its active metabolites and HCAs, carbamazepine, antipsychotics, or type IC antiarrhythmics than other SSRIs
	Sertraline	50–200	Of SSRIs, has highest incidence of loose stools
	Paroxetine	20–50	Withdrawal symptoms if discontinued abruptly
	Fluvoxamine	100–300	Can cause clinically significant elevation of theophylline, warfarin, and clozapine blood levels
Serotonergic-noradrenergic	Venlafaxine	75–375	Modest dose-dependent increase in diastolic BP
5-HT_2 antagonists	Trazodone	150–600	May cause priapism
	Nefazodone	200–600	Can cause serious cardiac arrhythmia with concurrent use of terfenadine or astemizole
	Mirtazapine	15–45	Causes weight gain
Catecholaminergic	Bupropion	150–450	Contraindicated in patients who have bulimia or who are seizure-prone

MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; HCAs = heterocyclic antidepressants; 5-HT_2 = 5-hydroxytryptamine (serotonin)$_2$.

tically. It can cause priapism (in 1 of 1000), which has not been reported with nefazodone. Unlike nefazodone, trazodone is an α_1-noradrenergic blocker and is associated with postural hypotension. It is extremely sedating, so its use in antidepressant doses (> 400 mg/day) is limited. It is most often used in small doses (50 to 100 mg at bedtime) to reverse insomnia due to SSRIs.

Mirtazapine blocks α_2-adrenergic autoreceptors as well as 5-HT_2 and 5-HT_3 receptors. The result is more efficient serotonergic function without sexual dysfunction and nausea. It has no adverse effects on cardiac function, has minimal interaction with drug-metabolizing liver enzymes, and is generally well tolerated, except for sedation and weight gain mediated by H_1 (histamine) blockade.

Heterocyclic antidepressants, the standard treatment for depression before 1990, include tricyclic (the tertiary amines amitriptyline and imipramine and their secondary amine metabolites nortriptyline and desipramine), modified tricyclic, and tetracyclic antidepressants. Acutely, these drugs primarily increase the availability of norepinephrine and, to some extent, of 5-HT by blocking reuptake in the synaptic cleft. Chronic administration down-regulates β_1-adrenergic receptors on the postsynaptic membrane—a possible final common pathway of their antidepressant activity. Like SSRIs, heterocyclic antidepressants are effective in 65% of clinically depressed patients. Although available data are equivocal, many clinicians believe that these drugs have an edge over the SSRIs in treating patients with melancholia and those hospitalized with depression.

The more common adverse effects of heterocyclic antidepressants derive from their muscarinic-blocking and α_1-adrenolytic actions. Most of these antidepressants are therefore unsuitable for patients with heart disease. Even small doses can cause tachycardia and quinidine-like effects on cardiac conduction. Desipramine can induce severe arrhythmias in children. Because heterocyclic antidepressants may cause postural hypotension, they are contraindicated in patients with osteoporosis, cerebral arteriosclerosis, or ischemic heart disease. Other common adverse effects include blurred vision, xerostomia, tachycardia, constipation, and urinary hesitancy (least with secondary amine tricyclic antidepressants). Sedation, depending on the need for sleep induction and maintenance, may or may not be considered an adverse effect and results largely from 5-HT_2 and H_1 blockade. Excessive weight gain occurs in some patients. Heterocyclic antidepressants, except for amoxapine, do not appreciably block D_2 (dopaminergic) receptors. Behavioral toxicity (excitement, confusion, hallucinations, or oversedation) is especially likely to occur in elderly patients with organic brain disease. All heterocyclic antidepressants, particularly maprotiline and clomipramine, lower the threshold for seizures.

Venlafaxine has a dual 5-HT and norepinephrine mechanism of action, as do tricyclic antidepressants, but its adverse effect profile is more benign, approximating that of SSRIs; nausea is the major problem during the first 2 wk. When dose is increased slowly (beginning with increments of 37.5 mg/day), venlafaxine is well tolerated, especially when the slow-release form is used. Venlafaxine may occasionally work faster (in < 1 wk) than other antidepressants. BP monitoring is recommended because diastolic BP increases in 3 to 5% of patients with doses > 225 mg/day. Venlafaxine has some advantages over SSRIs: It seems to work better in patients with severe or refractory depression, and because it is not highly protein bound and has virtually no interaction with drug-metabolizing liver enzymes, it poses little risk when given with other drugs.

Bupropion has no effects on the 5-HT system. By mechanisms not clearly understood, it favorably influences catecholaminergic, dopaminergic, and noradrenergic function. Bupropion is relatively free from cycling effects in bipolar depression. It can help depressed patients with concurrent attention-deficit hyperactivity disorder or cocaine dependence and those trying to stop smoking. Bupropion has no effects on the cardiovascular system but can produce seizures (in 0.4% of patients with doses > 450 mg/day); the risk is increased in patients with bulimia. It does not produce sexual adverse effects and interacts little with coadministered drugs. A common adverse effect is agitation, which is considerably attenuated with the slow-release form, making it easier to tolerate.

Monoamine oxidase inhibitors (MAOIs) inhibit the oxidative deamination of the three classes of biogenic amines—norepinephrine, dopamine, and 5-HT—and

in average doses) and an antidepressant with noradrenergic properties (eg, desipramine 50 to 75 mg/day); using high doses of venlafaxine, which combines both properties; combining a sedating tricyclic antidepressant (eg, amitriptyline 75 to 100 mg at bedtime) and an MAOI (eg, phenelzine 30 to 45 mg in the morning); and combining an MAOI and a stimulant (eg, dextroamphetamine, methylphenidate). The last two strategies should be used only by a mood disorder specialist because their safety and efficacy are problematic in inexperienced hands. Pindolol, a β-adrenergic blocker, is believed to boost the action of SSRIs and nefazodone via 5-HT_{1A} action; this experimental paradigm has not had consistently positive results.

Hospitalization: Persistent suicidal ideation (particularly when family support is lacking), stupor, agitated-deluded depression, physical debilitation, and concurrent severe cardiovascular disease require hospitalization and often electroconvulsive therapy. Severe suicidal, agitated, or retarded depression during pregnancy is best treated with electroconvulsive therapy. The response to 6 to 10 electroconvulsive treatments is usually dramatic and may be lifesaving. For psychotic depression that is less of an emergency, maximal doses of a venlafaxine or a heterocyclic antidepressant (eg, nortriptyline) can be given for 3 to 6 wk; if necessary, an antipsychotic (eg, thiothixene up to 20 mg/day po or IM in 2 or 3 divided doses) can be added. To reduce the risk of tardive dyskinesia, the physician should give the antipsychotic in the lowest effective dose and discontinue it as soon as possible. Atypical antipsychotics (eg, risperidone 4 to 8 mg/day, olanzapine up to 10 mg/day) appear relatively free of such risk and are being increasingly used. Continued therapy with an antidepressant for 6 to 12 mo (up to 2 yr in patients > 50 yr old) on an outpatient basis is ordinarily needed to prevent relapse in hospitalized patients treated with antidepressants and electroconvulsive therapy.

Maintenance therapy: Management of infrequent, recurrent depression is as for a single episode. However, depression recurs in 80% of patients, who must therefore receive long-term (possibly lifelong) antidepressant therapy. Dosage is often adjusted on the basis of mood level and adverse effects; however, in most patients, recurrence is best prevented by maintaining the full therapeutic dosage. There is no definitive evidence that antidepressants have teratogenic effects. If a pregnant woman has severe depression requiring maintenance therapy, she may take an antidepressant, but she should be carefully monitored by an obstetrician.

Patients with a family history of bipolar disorder must be observed for the development of hypomania; in such patients, maintenance therapy with lithium carbonate alone is probably equally effective. Relapses can occur even with the most rigorous maintenance therapy, and patients must be seen at least every 2 to 3 mo.

Psychotherapy: Supportive therapy and psychoeducation, formalized as depression-specific psychotherapies, are usually sufficient in enhancing pharmacologic treatment. Brief individual psychotherapy (with an interpersonal focus) or cognitive-behavioral therapy (individual or group) alone is effective in milder forms of depression. When used with antidepressants, these therapies are most useful after antidepressants have controlled melancholic signs. By providing support and guidance, by removing cognitive distortions that prevent adaptive action, and by encouraging the patient to gradually resume his social or occupational roles, these therapies may improve coping skills and enhance the gains made through pharmacotherapy. Couples' therapy may help diminish conjugal tensions and disharmony. Long-term psychotherapy is unnecessary except for patients who have long-term interpersonal conflicts in many areas of functioning or who are unresponsive to brief therapy.

DYSTHYMIC DISORDER

In dysthymic disorder, depressive symptoms typically begin insidiously in childhood or adolescence and pursue an intermittent or low-grade course over many years or decades; major depressive episodes may complicate it (double depression). In pure dysthymia, depressive manifestations occur at a subthreshold level and overlap considerably with those of a depressive temperament: habitually gloomy, pessimistic, humorless, or incapable of fun; passive and lethargic; introverted; skeptical, hypercritical, or complaining; self-critical, self-reproaching, and self-derogatory; and preoccupied with inadequacy, failure, and negative events.

Treatment

SSRIs are the treatment of choice. Secondary amine tricyclic antidepressants, especially desipramine, are also effective but may be more difficult to use because the dose should be high and adverse effects may compromise compliance. When the patient has a family history of bipolar disorder, lithium alone or with desipramine or bupropion is often effective. A trial with tranylcypromine may be worthwhile; moclobemide, a reversible MAOI unavailable in the USA, is reportedly effective and free of the problematic dietary and drug interactions of classic MAOIs. The antipsychotic amisulpride, a dopamine agonist unavailable in the USA, in low doses (25 to 50 mg/day) has been reported to be effective. The antipsychotic trifluoperazine 1 mg/day is roughly equivalent and may be used in refractory cases of severe dysthymia but only when its benefits outweigh the risk of tardive dyskinesia from long-term use.

Vocational counseling is important because many dysthymic persons are especially adept in work that involves dedication and painstaking attention to detail. Interpersonal and cognitive-behavioral psychotherapies are being increasingly used to combat the inertia and self-defeating mental set of these patients; such therapies are best combined with pharmacotherapy.

BIPOLAR DISORDERS

Thorough evaluation of many persons with depression reveals bipolar traits, and as many as one in five patients with a depressive disorder also develops frank hypomania or mania. Most switches from unipolar to bipolar disorder occur within 5 yr of the onset of depressive manifestations. Predictors of a switch include early onset of depression (< 25 yr old), postpartum depression, frequent episodes of depression, quick brightening of mood with somatic treatments (eg, antidepressants, phototherapy, sleep deprivation, electroconvulsive therapy), and a family history of mood disorders for three consecutive generations.

Between episodes, patients with bipolar disorder exhibit depressive moodiness and sometimes high-energy activity; disruption in developmental and social functioning is more common than in unipolar disorder. In bipolar disorder, episodes are shorter (3 to 6 mo), age of onset is younger, onset of episodes is more abrupt, and cycles (time from onset of one episode to that of the next) are shorter than in unipolar disorder. Cyclicity is particularly accentuated in rapid-cycling forms of bipolar disorder (usually defined as ≥ 4 episodes/yr).

In **bipolar I disorder,** full-fledged manic and major depressive episodes alternate. Bipolar I disorder commonly begins with depression and is characterized by at least one manic or excited period during its course. The depressive phase can be an immediate prelude or aftermath of mania, or depression and mania can be separated by months or years.

In **bipolar II disorder,** depressive episodes alternate with hypomanias (relatively mild, nonpsychotic periods of usually < 1 wk). During the hypomanic period, mood brightens, the need for sleep decreases, and psychomotor activity accelerates beyond the patient's usual level. Often, the switch is induced by circadian factors (eg, going to bed depressed and waking early in the morning in a hypomanic state). Hypersomnia and overeating are characteristic and may recur seasonally (eg, in autumn or winter); insomnia and poor appetite occur during the depressive phase. For some persons, hypomanic periods are adaptive because they are associated with high energy, confidence, and supernormal social functioning. Many patients who experience pleasant elevation of mood, usually at the end of a depression, do not report it unless specifically questioned. Skillful questioning may reveal morbid signs, such as excesses in spending, impulsive sexual escapades, and stimulant drug abuse. Such information is more likely to be provided by relatives.

Patients with major depressive episodes and a family history of bipolar disorders (unofficially called **bipolar III**) often exhibit subtle hypomanic tendencies; their temperament is termed **hyperthymic** (ie, driven, ambitious, and achievement-oriented).

Symptoms and Signs

Symptoms of the depressive phase are similar to those of unipolar depression (see above), except that psychomotor retardation, hypersomnia, and, in extreme cases, stupor are more characteristic.